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Human cells from cloned embryos in research and therapy

Current methods of cloning are repeatable but remain inefficient

News p 421

The recent report of the derivation of stem cells from a cloned human embryo takes a small, but significant, step towards revolutionary new opportunities in biology and medicine.[1] By developing these techniques it will become possible to study human genetic diseases in entirely new ways, before in the longer term such cells may be used in the treatment of human disease. However, much remains to be learned about the techniques that are required before these opportunities can be realised. Furthermore, as with all new technical developments, experience will be needed to learn how such cells should best be used.

The procedure that was used in the Korean experiment was essentially the same as that used to produce Dolly, the cloned sheep.[2] During a series of trials a total of 30 of the 242 cloned embryos developed normally for six days to reach the blastocyst stage before attempts were made to derive embryo stem cells.[1] Cells were isolated from 20 of these embryos, and from these one stable cell line was derived. As would be expected of embryo stem cells, they had the ability to grow for a prolonged period in culture and to form other cell types. These yields are impressive for an early study, but improvement in efficiency will be required for practical application.

Studies of human genetic diseases

Cells from cloned embryos will create new opportunities to study genetic diseases in which the gene(s) involved has not been identified. The disease that is variously known as motor neurone disease, amyotropic lateral sclerosis, or Lou Gehrig's disease is one such case. Degeneration of motor neurones is the common cause of this fatal condition, but the cause of the disease is not fully understood.[3] Several genetic and environmental factors seem to contribute to the pathogenesis of motor neurone disease, although the causes of the degeneration are not understood.

Most cases of motor neurone disease are sporadic, but 5-10% are inherited. Among these familial cases mutations in the gene that encodes superoxide dismutase (SOD1) account for approximately 20% of cases, and genetic analysis indicates that at least four other genes remain to be identified.[4] The cause of motor neurone disease was at first assumed to be reduced function of the gene, but this seems not to be the case. Mice in which the endogenous SOD1 gene has been deleted do not develop motor neurone disease, whereas those that express mutant forms of the human gene develop paralysis.[5] As the transgenic mice carrying the human gene also had their own two copies of the gene this observation implies that the effect of the mutation is through a cytotoxic effect of the abnormal protein, rather than a loss of function.

There are several new potential sources of cells liable to motor neurone disease that may reveal the means by which this protein causes neurodegeneration. If pre-implantation genetic screening is practised for those cases in which the mutation has been identified then embryo stem cells could be derived from those embryos identified as carrying the mutation. Alternatively, known mutations could be introduced into embryo stem cells derived from embryos not known to be liable to motor neurone disease and subsequently the motor neurone disease cells contrasted with the original line. However, these approaches are only available in the cases in which the mutation has been identified—approximately 2% of cases. In an additional 8% of cases, the condition is inherited, but the mutation has not been identified. Nuclear transfer may offer new opportunities in this situation.

Cells for therapy

Cells derived from embryo stem cells offer the hope of new treatments for some very unpleasant degenerative diseases including cardiovascular disease, spinal cord injury, Parkinson's disease, and type 1 diabetes. Methods for the derivation of specific cell types from stem cells lines are being established, although in most cases we have still not confirmed that they function normally after transfer. In addition a great deal remains to be learnt about the most effective means of introducing the cells into patients.

In any treatment regime we must avoid immunological rejection of the transferred cells, but the immune response is likely to vary from one disease to another. Cells from cloned embryos would be most valuable in conditions such as cardiovascular disease in which immune rejection could be avoided by transfer of histocompatible cells. By contrast, in the treatment of diseases within the central nervous system cells from cloned embryos seem likely to offer less advantage as fetal cells in the central nervous system appear not to be subject to rejection.[6,7] Finally, several of the conditions that are mentioned as candidates for cell therapy are autoimmune diseases, including type 1 diabetes. In such cases transfer of immunologically

BMJ 2004;328:415–6

identical cells to a patient is expected to induce the same rejection.

At present methods of cloning are repeatable and used by many laboratories around the world. However, they are inefficient. Typically only 0-5% of cloned embryos become viable offspring, regardless of species, method of nuclear transfer, choice of donor cells, or species.[8] This low overall efficiency reflects a failure of current procedures to reprogramme the patterns of gene expression from those appropriate for an adult cell to that required for normal development of an embryo.[9] Whether similar abnormalities in gene expression would occur in embryo stem cells derived from cloned embryos is not known. In these circumstances it would seem sensible for the first use of cells from cloned embryos to be in research.

Considerable differences exist between countries in the regulation of nuclear transfer to produce human embryos. In the United Kingdom, projects to derive cells from cloned embryos may be approved by the regulatory authority for the study of serious diseases. By contrast human reproductive cloning would be illegal. Several debates have taken place at the United Nations on these subjects. One group of countries, led by the United States, proposed a complete ban on human nuclear transfer, whereas the others wish to allow production of cells from cloned embryos. The issue is due to be revisited again in the near future.

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Competing interests: IW has been a consultant to Geron Corporation, Menlo Park, USA, has shares in the company, and has received funds to support research in his laboratory.

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Patients' expectations of consultations

Patient pressure may be stronger in the doctor's mind than in the patient's

Primary care pp 441, 444

Although patients' expectations of general practice consultations influence outcomes, they are not as influential as doctors' assessments. This may sound obvious except for the fact that doctors' assessments of patients' preferences have more influence than those preferences themselves. In this issue Little et al are publishing two studies.[1 2] Their observational study generalises the finding from an earlier study[3] that doctors' perceptions are a stronger predictor of their actions—from prescribing to other consultation activities—than are patients' expectations. The same factors (including doctors' perceptions) affecting prescribing decisions also affect other clinical decisions. This makes it all the more important that doctors' perceptions are accurate. Inappropriate assessments of patients' expectations can result in actions deemed unnecessary by the doctor and unwanted by the patient.

In their interventional study Little et al used leaflets and found that most of the increased investigations resulting from the intervention were not felt by either the doctor or the patient to be strongly needed. Another observational study about prescribing decisions showed that some prescriptions wanted by the patient but thought not to be strictly indicated by the doctor were not taken as prescribed.[4]

These studies and others show that doctors do things they consider unnecessary in a noteworthy minority of cases. What is going on? When asked, some doctors state that they write prescriptions that are not clinically needed, in order to maintain relationships with their patients.[5] Perhaps the key to the issue is the notion of pressure. In the observational study by Little, as in other studies, doctors were asked if they felt pressurised by patients.[1] The patients were asked, in a pre-consultation questionnaire, whether they wanted a prescription, referral, and so on. If patients indicated on the questionnaire that they wanted a particular outcome, this was described as "direct pressure." What is not known from any of these studies is whether patients who endorse a questionnaire item—stating that they want an investigation, for example—say so in the consultation. We know from other observational studies of the consultation that patients do not voice all their agenda items and that requests tend to be indirect.[6 7] We also know that doctors make assumptions about patients' preferences that may not be accurate and that doctors can display more certainty about their perceptions of patients' preferences than the patients themselves. In a study of 161 general practice consultations Jenkins et al found that patients were much more uncertain about their preferences for prescriptions than doctors perceived them to be. Patients expressed uncertainty in 60 instances; doctors in only 13.[8]

All this implies that pressure from patients may be stronger in the doctor's mind than in the patient's

BMJ 2004;328:416–7